Essential Prescribing Information (EPI)

1. Introduction and Background Information

CAUTION : Federal (USA) Law restricts this device to the sale by or on the order of a physician (or properly licensed practitioner).

1.1. Description of the device

UBIS 5000 (Ultrasound Bone Scanner) is a quantitative ultrasound (QUS) bone sonometer which measures bone properties at the calcaneus using non-audible high-frequency sound waves. The device consists of a dedicated PC, water-bath scanner, and accessories.

The UBIS 5000 measurements are made with the patient seated in a chair without wheels, in front of the device with her/his foot placed in thefootwell. The heel is surrounded by approximately 0.35 liters of water (replaced after each scan) heated to approximately 30°C (86°F). The water is an optimum medium for the transmission of ultrasound. A focused transducer on one side of the heel converts an electrical signal into a sound wave which passes through the water and the patient's heel. A second focused transducer on the opposite side of the patients heel receives the sound wave and converts it into an electrical signal that is analyzed by the UBIS 5000 software. This is repeated a total of 3600 times to provide a scanning area of 60mm x 60mm. UBIS 5000 software thus creates an image scan of the complete calcaneus, from which a specific ROI (a 14 mm diameter circle) is automatically selected, based on the area of lowest attenuation. This allows UBIS to adapt the region of interest to the anatomy of each patient, and avoids inconsistent readings that are possible with a system using fixed transducers.

The results are given as broadband ultrasound attenuation (BUA, in dB/MHz). This ultrasound parameter is based on the frequency dependent attenuation, with the higher BUA values corresponding to lower risk of fracture, and vice versa.

Before the BUA measurement can be used for a diagnosis it needs to be compared to the average value of the young normal Caucasian females. This comparison is done using an index called T-score, which represents the BUA value on a normalized scale. T-score above (below) 0 corresponds to a bone stronger (weaker) than that of the average young normal Caucasian women. The T-score is the recommended parameter for assessing the risk of fracture.

Comparing the actual BUA value to the average value in a healthy population of the same gender, ethnic origin, and age, when expressed in terms of standard deviations (SDs) of that population, is called Z-score, which can be used as an aid in the detection of conditions associated with non-age-related bone loss.

1.2. Indications For Use

The UBIS 5000 is a quantitative ultrasound (QUS) bone sonometer to be used for the measurement of broadband ultrasound attenuation (BUA) of the calcaneus, as an aid to diagnose osteoporosis and to estimate the risk of subsequent atraumatic fracture. The output is expressed in terms of both BUA and T-score.

1.3. Contraindications

None.

1.4. Warnings

1. Do not use on a foot that has ever had a heel fracture.
2. Do not use on a foot with edema (excess water/swelling).
3. Do not use on a foot with any skin abrasion.
4. Do not use on patients with leg paralysis.
5. Do not use on patients with a lower extremity prosthesis.
6. Do not use on patients under the age of 20, as there is no reference database available for this age group.
7. Patients must not move their foot during the scanning operation. Such movement can cause inaccuracies in both the image and the BUA measurement.
8. Change the water and process the footwell between patients following the cleaning and disinfection instructions.

1.5. Precautions

1. Users should read the Operators Manual before prescribing UBIS 5000, or interpreting the results.UBIS 5000 should always be switched ON/OFF using the Main Switch located at the rear of the Scanner. Do NOT switch off individually the PC, the Monitor, or the Printer.
2. Use the UBIS 5000 only indoors, in a clean dry environment. Failure to do so could result in unsatisfactory results.
3. Do not store the UBIS 5000 near either a heat source or air conditioner.
4. The UBIS 5000 should not be moved while there is water in the footwell, as this may cause spillage into the interior of the machine.
5. Use only DMS-approved Ultrasound Solution.
   - This product is irritating to the eyes and skin when it is undiluted. In case of direct contact with either the eyes or skin, immediately wash off with water and ask your physician for special advice.
   - Always rinse your hands immediately after use.
   - In case of ingestion, do not make the person vomit and immediately call for a physician and show the cover or label of the product.
   - Do not use in combination with other products. Toxic gas (chlorine) might be released.

6. Do not use this equipment in the presence of a flammable anesthetic, oxygen, or nitrous oxide.
7. The UBIS 5000 must not be cleaned with abrasive materials, as this will cause damage to the ultrasound probes.
8. All interfacing equipment (monitor, printer) must meet with IEC 60601-1 or equivalent electrical standards.
9. Do not use portable cellular equipment (walkie-talkies, radio phones, portable telephones) in the proximity of the UBIS 5000 during its operation, as this may impact the accuracy of the measurements.
10. In order to avoid electrical shocks, do not remove the cover from the UBIS 5000. The UBIS 5000 contains no user-serviceable parts.

1.6. Adverse Events

None known.

1.7. Maintaining Device Effectiveness

The physician/operator should routinely clean the UBIS 5000 with non-abrasive materials. The Quality Control test is automatically carried out before each examination on an internal phantom. Graphic and statistic display of the results can be accessed from the main menu. The physician/operator does not have access to the internal parts of the device.

1.8. Patient Counseling Information

Supplied with the UBIS 5000 are patient brochures titled "Information for Patients." These documents can be freely re-duplicated or can be ordered from DMS.

Further information on osteoporosis can be obtained from *National Osteoporosis Foundation, 1150 17th Street, N. W. Suite 500, Washington , D. C. 20036-4603, Tel : (202) 223-2226.*

1.9. How the UBIS 5000 is supplied

The UBIS 5000 is supplied as a complete operational unit, with a dedicated computer and all the accessories required to operate it. The monitor and the printer may be supplied by either the customer or by DMS.

2. Clinical Studies

Clinical studies were conducted to assess the safety and effectiveness of the UBIS 5000, a quantitative ultrasound bone sonometer device, as an aid to establish the diagnosis of osteoporosis and to identify patients with high risk of osteoporotic fracture. These clinical studies were aimed at meeting the following objectives:

- To establish a U.S. Reference Database for the BUA of UBIS 5000 on healthy or non-fractured Caucasian U.S. women aged 20 to 79 ("Reference Database Study").
- To estimate the in-vivo short-term precision of the BUA obtained by UBIS 5000 ("Precision Study").
- To establish the capacity of UBIS 5000 BUA, a) to assess the risk of fracture, b) to discriminate between patients who have suffered atraumatic fractures and age-matched control subjects who have never had an atraumatic fracture, and c) to compare the performance of the device with those of one DEXA and two QUS systems, in order to assess possible bias in selection of control patients ("Fracture Risk Studies").

Clinical studies were carried out in two U.S. centers, located in Massachusetts and California, and in one European center, located in Switzerland. The same protocol was followed in all the centers.

2.1 Reference Database Study

Four hundred seven (407) healthy Caucasian U.S. females, ranging in age from 20 to 79 years, were used to establish the normality curve. A segmental linear regression analysis based on a moving average over ten years of range with a step of five years gave the following result for the normality curve:

From 20 to 50 years old, $\mathbf{BUA = 0.0066Age_j + 64.573}$
From 51 to 59 years old, $\mathbf{BUA = -0.3088Age_j + 80.538}$
From 60 to 79 years old, $\mathbf{BUA = -0.0746Age_j + 66.585}$

The Normality Curve of UBIS 5000 BUA for Caucasian U.S. Women is displayed in Figure 1, showing that between 50 and 59 years old (post menopause) the BUA declines by 2.8 dB/MHz (i.e., around 65% of the range). Then, between 60 and 79 years old, the BUA significantly declines by an average of 0.75 dB/MHz per decade (i.e., around 17% of the range).

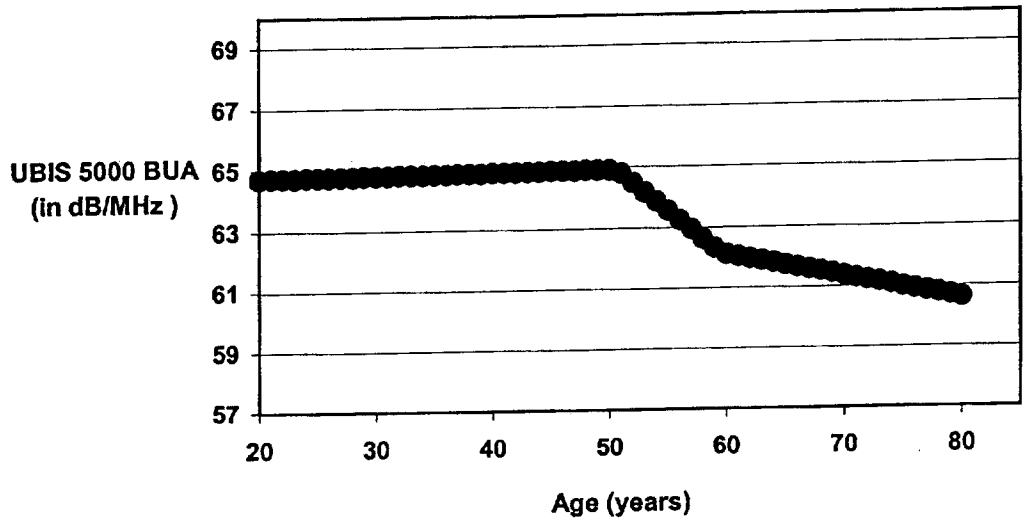

Figure 1- *Normality Curve of UBIS 5000 BUA for Caucasian U.S. Women*

The 20-39 age range was selected for the representative sample of the young normal Caucasian U.S. female reference population. This young reference population's mean BUA, as well as its standard deviation (SD), were calculated for the purpose of generating T-scores. (see Table 1)

	Value	95% Confidence Interval
Mean BUA UBIS 5000	64.8	64.2 – 65.4
Standard Deviation	4.1	3.3 - 4.8

Table 1- *Young Reference Value for UBIS 5000 BUA (Data From 171 U.S. Caucasian Females, Ages 20 to 39)*

Given the previous results, the T-score of the patient "j" is calculated as follows:

$$T-score_j = \frac{BUA_j - 64.8}{4.1}$$ where BUA_j is the BUA measured on the patient "j".

In order to calculate the Z-score, the SD of the BUA for the 50-79 age group was calculated: $SD_{50\text{-}79} = 5.0$ dB/MHz. The Z-score of patient "j" is calculated as follows:

From 40 to 50 years old, $Z-score_j = \frac{BUA_j - 0.0066\,Age_j - 64.573}{5.0}$

From 51 to 59 years old, $Z-score_j = \frac{BUA_j + 0.3088\,Age_j - 80.538}{5.0}$

From 60 to 79 years old, $Z-score_j = \frac{BUA_j + 0.0746\,Age_j - 66.585}{5.0}$

where Age_j is the age of the patient "j".

2.2 Precision Study

Fifty-eight (58) subjects ranging in age from 20 to 79 were recruited by the two U.S. centers and used to assess the measurement reproducibility. Each subject was examined three times with UBIS 5000, with foot repositioning before each examination.

Precision was evaluated by calculating the RMS SD, the RMS CV, the CV, the SCV, $longPE_{cc}$, and the TSD. (See section 18 of the User Manual for definitions.) Results are displayed in Table 2.

	BUA UBIS 5000®
RMS SD	0.41 dB/MHz
RMS CV	0.65 %
CV	0.50 %
SCV	2.18 %
$LongPE_{cc}$	3.1 years
TSD	0.10

Table 2- *Results of the Evaluation of the UBIS 5000 Precision (58 American Subjects Aged between 20 to 79)*

2.3 Correlation Study

Fifty-four subjects ranging in age from 20 to 79 where enrolled by the California center. Each subject had an examination on the same foot with the UBIS 5000 as well as with a LUNAR PIXI according to the correspondent Operator's Manual.

Results showed that UBIS 5000 BUA and Heel BMD obtained with LUNAR PIXI were correlated with a correlation coefficient of Pearson equal to **r=0.89**.

2.4 Fracture Risk Studies

Two fracture risk studies were independently carried out in the Swiss and California centers.

Table 3 show that the UBIS 5000 measurements for the fractured subjects, when expressed in T-score or in Z-score, are similar to Neck or Spine BMD, or to QUI and Stiffness results.

	Controls	Fractured	Z-score	T-Score
BUA UBIS 5000	61.5 ± 5.0	57.2 ± 4.8	-0.8	-1.9
Neck BMD	0.694 ± 0.111	0.614 ± 0.111	-0.6	-1.5
Spine BMD	0.954 ± 0.141	0.839 ± 0.141	-0.7	-2.1

Table 3- *California Center, UBIS 5000 and DEXA Parameters of the Two Groups Expressed in Z-score and T-score*

	Controls	Fractured	Z-score	T-Score
BUA UBIS 5000	60.4 ± 5.1	54.6 ± 4.9	-1.1	-2.5
QUI (Hologic)	75.9 ± 16.1	57.4 ± 17.8	-1.2	-2.4
Stiffness (Lunar)	72.7 ± 12.7	57.1 ± 12.2	-1.2	-2.6

Table 4- *Swiss Center, UBIS 5000 and QUS Parameters for the Two Groups Expressed in Z-score and in T-score*

For each center, non-adjusted and adjusted Odds Ratios per standard deviation decrease were estimated, with their 95% confidence intervals, and the areas under the ROC curves were obtained (see Tables 5 and 6).

	Non-Adjusted Odds Ratios (95% CI)	Adjusted Odds Ratios* (95% CI)	Area under the ROC Curve** (95% CI)
BUA UBIS 5000	**2.55** (1.55 - 4.20)	**1.84** (1.15 - 3.37)	**0.73** (0.62 - 0.81)
Neck BMD	**2.25** (1.36 - 3.72)	**1.69** (1.05 - 3.01)	**0.71** (0.61 - 0.81)
Spine BMD	**2.40** (1.48 - 3.87)	**2.23** (1.37 - 3.86)	**0.74** (0.63 - 0.82)

*Adjusted by Age, Weight and Height.
**Not Adjusted by age.

Table 5- *California center, Odds Ratios per Standard Deviation Decrease and Area under the ROC Curve for each Bone Parameters*

	Non-Adjusted Odds Ratios (95% CI)	Adjusted Odds Ratios* (95% CI)	Area under the ROC Curve** (95% CI)
BUA UBIS 5000	**3.74** (2.12 - 6.60)	**3.15** (1.57 - 6.31)	**0.81** (0.72 - 0.88)
QUI HOLOGIC	**3.92** (2.11 - 7.26)	**2.89** (1.39 - 5.98)	**0.82** (0.73 - 0.89)
Stiffness LUNAR	**4.62** (2.43 - 8.79)	**3.70** (1.77 - 7.71)	**0.82** (0.73 - 0.89)

*Adjusted by Age, Weight and BMI.
**Not Adjusted by age.

Table 6- *Swiss Center, Odds Ratios per Standard Deviation Decrease and Area under the ROC Curve for each Bone Parameters*

ROC curves as well as Odds Ratios analysis showed no statistical difference between UBIS 5000 and DEXA technique or QUS systems, thus demonstrating the absence of any significant bias in selection of control patients, and also demonstrating the ability of the UBIS 5000 to discriminate between fractured subjects and controls.

3. Individualization of Treatment

The UBIS 5000 is suitable for T-score determinations of adults of any ethnicity, age, or gender, however all patients are to be referred to the young normal Caucasian U.S. female reference database. The UBIS 5000 is suitable for Z-score determinations of Caucasian women only, since this is the only reference data base provided, and since Z-score, unlike T-score, requires comparison to non-fractured subjects of the same age, ethnicity, and gender.

4. System Safety / Conformance to standards

The UBIS 5000 conforms to International Standards for safety and electromagnetic compatibility. This device uses ultrasound power levels lower than standard imaging ultrasound devices which are widely used and accepted (See 4.2 Ultrasound Radiation below).

4.1. Voluntary Standard Compliance

UBIS 5000 complies with :
IEC 60601-1 (General Requirements for Electrical Safety)
IEC 60601-1-2 (General Requirements for Electromagnetic Compatibility)

4.2. Ultrasound Radiation

Three ultrasound transmitting/receiving probes were tested in accordance with the Track 1 of the American Food and Drug Administration (FDA) document 510k, entitled "Measuring and Reporting Acoustic Output of Diagnostic Ultrasound Medical Devices", 1985.

	Probe 1	Probe 2	Probe 3	Typical uncertainty (+/-)
MI	0.24	0.27	0.20	20%
$p_{.3}$ (Mpa)	0.16	0.18	0.14	13%
I_{SPPA} ($W.cm^{-2}$)	190	170	100	26%
I_{SPTA} ($mW.cm^{-2}$)	240	210	131	25%
Beam diameter (cm)	0.72	0.73	0.77	7%